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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/52, 31/41, 31/19

A1

(11) International Publication Number: WO 98/42346

(43) International Publication Date: 1 October 1998 (01.10.98)

(21) International Application Number: PCT/US98/05478

(22) International Filing Date: 19 March 1998 (19.03.98)

(30) Priority Data:
60/041,572 21 March 1997 (21.03.97) US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: LEUKOTRIENE ANTAGONISTS USEFUL FOR TREATING ISCHEMIA REPERFUSION INJURY

(57) Abstract

This invention provides methods for the treatment or inhibition of ischemia reperfusion injury which comprises administering to a mammal in need thereof an effective amount of a compound having activity as a leukotriene B_4 antagonist.

LEUKOTRIENE ANTAGONISTS USEFUL FOR TREATING ISCHEMIA REPERFUSION INJURY

During focal ischemia, the extent of parenchymal tissue damage relates closely to two factors: the level of blood flow during the ischemic interval and the duration of ischemia.

On return of blood flow, there is a resumption of the principal functions of tissue perfusion: oxygen delivery, provision of substrates for metabolism, and clearance of metabolic wastes. The restored perfusion counteracts the ischemic injury process and serves to return at least some of the reversibly injured tissue to a functional state.

However, there is a developing consensus that return of blood flow in the postischemic period has a dark side. Interactions between blood and damaged tissue can lead to further tissue injury. It is likely that unmodified blood is not an ideal perfusate for reflow to tissue subjected to prior ischemia. Its reintroduction can actually contribute to parenchymal cell loss as an unwanted side effect of its more familiar capacity to salvage reversibly damaged cells.

This paradoxically harmful aspect of blood flow return has been termed *reperfusion injury* and the process has potential relevance to clinical medicine. Although reperfusion per se is essential to functional recovery and reduces the volume of tissue infarcted, a further reduction in tissue loss might be achieved by measures that counteract reperfusion injury.

Virtually every organ undergoing ischemic insult may be subjected to reperfusion injury, although much of the work on these phenomena has been done in heart and brain. Concepts of reperfusion injury tend to emphasize similarities between mechanisms of cell death in various tissues rather than properties unique to a given tissue.

Early research on myocardial reperfusion suggested that reperfusion may accelerate the development of necrosis in

irreversibly injured myocytes. An ultrastructural appearance of "explosive swelling," was noted which included architectural disruption, contraction bands, and intermitochondrial calcium phosphate granules.

Later studies reported the paradox of myocardial necrosis after successful revascularization by coronary artery bypass graft surgery and suggested that the lesions were operation related and represented contracture due to calcium loading and myocardial cellular edema in the distribution of widely patent arterial grafts. The studies further concluded that prevention of intraoperative myocardial injury must also focus on characteristics of the phase of myocardial reperfusion.

Additional demonstrated that measures instituted after the termination of ischemia, which attenuated the rise in myocardial cytosolic calcium, led to a reduction of tissue injury. Subsequently, other workers have implicated cell swelling, white blood cell plugging of vessels, and free radical damage in reperfusion injury of the heart.

Research also focused attention on the contribution of reperfusion impairment to neural injury. Based on a disproportionately long survival of retinal ganglion cells exposed to anoxia in culture (in which oxygen could diffuse directly to the cells when reintroduced rather than requiring an intact tissue perfusion) as compared with the rapidity with which ischemia in vivo leads to irreversible brain cell damage, they postulated that recirculation of ischemic brain could become compromised and account for the differences in neuronal vulnerability observed under the two conditions.

This impairment of microvascular reperfusion was attributed primarily to two phenomena. The first was narrowing of the capillary lumen due to perivascular swelling and formation of endothelial blebs, and the second was increased blood viscosity. Fluid shifts into cells, with their sodium-potassium adenosine triphosphatase pumps shut down by energy failure, were thought to underlie both

the capillary narrowing and the microvascular hemoconcentration with increased blood viscosity. In addition, others described the topography of "no reflow," and published provocative studies that have demonstrated the resumption of function in cortical neurons after total ischemia for periods of 30 minutes to 1 hour if measures were taken to overcome reperfusion impairment.

The concept of a multifocal impairment of reflow manifesting immediately after ischemia and decreasing with time was modified and extended by consideration of "autodestruction" in models of spinal cord trauma and reperfusion problems encountered during autotransplantation of organs preserved by ex vivo perfusion.

Returning blood flow was viewed as having two dichotomous effects: (1) a well-established restorative effect and (2) a postulated capacity to undergo a multifactoral interaction with damaged tissue that could progressively shut down microcirculatory flows and contribute to further neuronal damage.

Studies measuring blood flow and metabolism in gerbils subjected to unilateral carotid occlusion, noted an immediate return of perfusion to the brain on release of the occlusion, following in 10 to 30 minutes by a decline in flow for at least 4 hours with a coincident rise in the cerebral metabolic rate that disrupted the normal flow-metabolism couple. This phenomenon was later documented in the four-vessel occlusion model that they had devised in rats.

Consideration of blood elements, blood vessels, and blood flow during and after ischemia is also derived from work in endothelial cell tissue culture. Recent evidence indicates that endothelial cells produce superoxide under certain circumstances. This may have a major role in reperfusion injury.

Calcium has been implicated in reperfusion injury under several circumstances. Reperfusion can cause an acute acceleration of calcium influx into cells by injuring cell

membranes with a consequent increased membrane permeability. The exact role of cytosolic calcium accumulation in the evolution of neuronal and myocardial injury after ischemia remains to be elucidated, but there is considerable evidence that ischemia and reperfusion are associated with a severe disruption of calcium homeostasis.

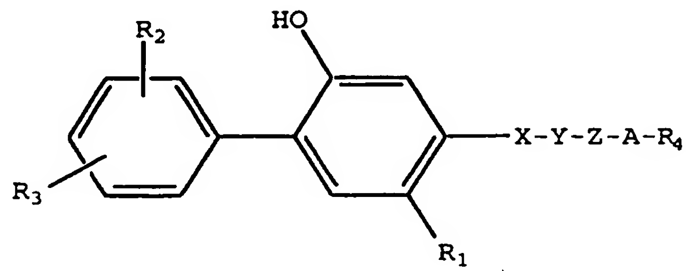
Generally, reperfusion of ischemic tissues is associated with endothelial cell injury, inflammatory cell infiltration and microvascular dysfunction. "Reperfusion injury" has been attributed to leukocytes and their ability to increase free radicals, cytotoxic enzymes and affect blood rheology. However, providing blood soon to ischemic tissue is, of course, beneficial.

Research in the area of allergic reactions of the lung has provided evidence that arachidonic acid derivatives formed by the action of lipoxygenases are related to various disease states. Some of these arachidonic acid metabolites have been classified as members of a family of eicosatetraenoic acids termed leukotrienes. Three of these substances are currently thought to be major components of what has been previously called slow reacting substance of anaphylaxis (SRS-A) and have been designated leukotrienes C_4, D_4, and E_4 (LTC_4, LTD_4, and LTE_4, respectively).

Another arachidonic acid metabolite, leukotriene B_4 (LTB_4), is a proinflammatory lipid which has been implicated in the pathogenesis of psoriasis, arthritis, chronic lung diseases, acute respiratory distress syndrome, shock, asthma, inflammatory bowel diseases, and other inflammatory states characterized by the infiltration and activation of polymorphonuclear leukocytes and other proinflammatory cells. Thus activated, the polymorphonuclear leukocytes liberate tissue-degrading enzymes and reactive chemicals causing the inflammation. Antagonism of LTB_4 should therefore provide a novel therapeutic approach to treatment of these and other LTB_4 mediated conditions.

Because of the debilitating effects of ischemia reperfusion injury, there continues to exist a need for effective treatments.

This invention provides a method for the treatment or inhibition of ischemia reperfusion injury in a mammal comprising administering to a mammal in need thereof an effective amount of a compound of the Formula I



I

wherein:

R_1 is C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, C_1-C_4 alkoxy, (C_1-C_4 alkyl)thio, halo, or R_2-substituted phenyl;

each R_2 and R_3 are each independently hydrogen, halo, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, (C_1-C_4 alkyl)-S(O)$_q$-, trifluoromethyl, or di-(C_1-C_3 alkyl) amino;

X is -O-, -S-, -C(=O), or -CH_2-;

Y is -O- or -CH_2-;

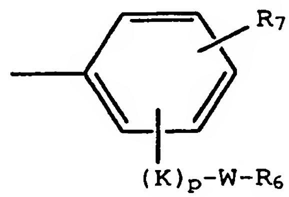
or when taken together, -X-Y- is -CH=CH- or

$$—C\equiv C—$$;

Z is a straight or branched chain C_1-C_{10} alkylidenyl;

A is a bond, -O-, -S-, -CH=CH-, or $-CR_aR_b-$, where R_a and R_b are each independently hydrogen, C_1-C_5 alkyl, or R_7-substituted phenyl, or when taken together with the carbon atom to which they are attached form a C_4-C_8 cycloalkyl ring;

R_4 is R_6 ,



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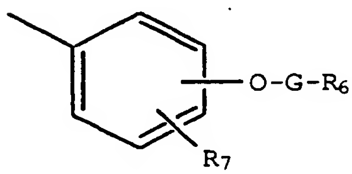

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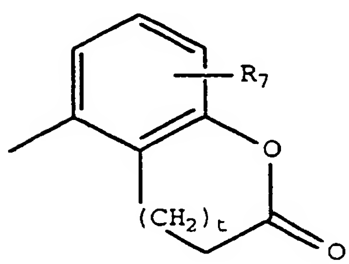

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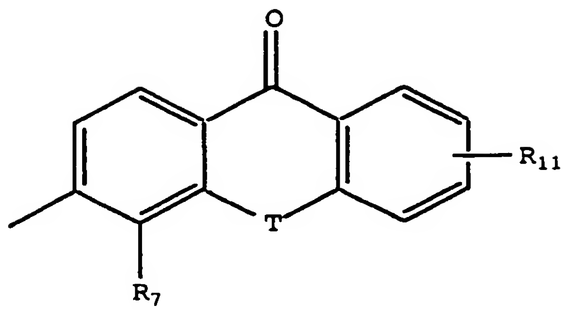

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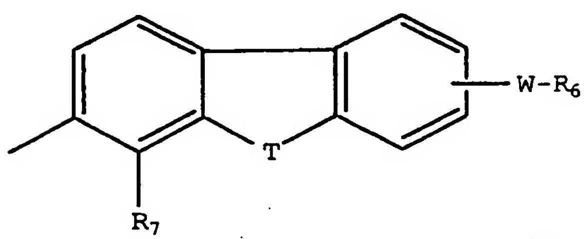

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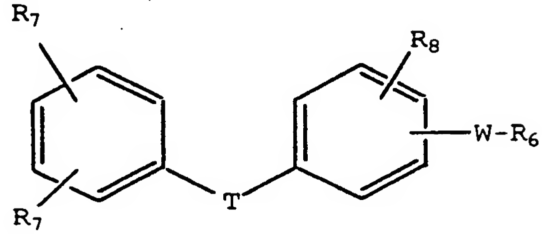


where,

each R_6 is independently -COOH, 5-tetrazolyl, $-CON(R_9)_2$, or $-CONHSO_2R_{10}$;

each R_7 is hydrogen, C_1-C_4 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, benzyl, methoxy, $-W-R_6$, $-T-G-R_6$, (C_1-C_4 alkyl)-T-(C_1-C_4 alkylidenyl)-O-, or hydroxy;

R_8 is hydrogen or halo;

each R_9 is independently hydrogen, phenyl, or C_1-C_4 alkyl, or when taken together with the

nitrogen atom form a morpholino, piperidino, piperazino, or pyrrolidino group;

R_{10} is C_1-C_4 alkyl or phenyl;

R_{11} is R_2, -W-R_6, or -T-G-R_6;

each W is a bond or straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

each G is a straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

each T is a bond, -CH_2-, -O-, -NH-, -NHCO-, -C(=O)-, or -S(O)$_q$-;

K is -C(=O)- or -CH(OH)-;

each q is independently 0, 1, or 2;

p is 0 or 1; and

t is 0 or 1;

provided when X is -O- or -S-, Y is not -O-;

provided when A is -O- or -S-, R_4 is not R_6;

provided when A is -O- or -S- and Z is a bond, Y is not -O-; and

provided W is not a bond when p is 0;

or a pharmaceutically acceptable salt or solvate thereof.

The following definitions refer to the various terms used throughout this disclosure.

The term "C_1-C_5 alkyl" refers to the straight and branched aliphatic radicals of 1 to 5 carbon atoms such as methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, 2,2-dimethylpropyl, and the like. Included within this definition are the terms "C_1-C_3 alkyl", and "C_1-C_4 alkyl".

The term "C_2-C_5 alkenyl" refers to straight and branched aliphatic radicals of 2 to 5 carbon atoms containing one double bond, such as $-CH{=}CH_2$, $-CH_2CH{=}CH_2$, $-CH_2CH_2CH{=}CH_2$, $-CH_2C(CH_3){=}CH_2$, $-CH_2CH{=}C(CH_3)_2$, and the like.

The term "C_2-C_5 alkynyl" refers to straight and branched aliphatic residues of 2 to 5 carbon atoms containing one triple bond, such as $-C{\equiv}CH$, $-CH_2-C{\equiv}CH$, $-CH_2CH_2C{\equiv}CH$, $-CH_2CH(CH_3)C{\equiv}CH$, $-CH_2C{\equiv}CCH_3$, and the like.

The term "C_1-C_4 alkoxy" refers to methoxy, ethoxy, propoxy, isopropoxy, butoxy, sec-butoxy, and tert-butoxy.

The term "halo" refers to fluoro, chloro, bromo, and iodo.

The term "C_1-C_{10} alkylidenyl" refers to a divalent radical derived from a C_1-C_{10} alkane such as $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH(C_2H_5)-$, $-CH_2CH_2-$, $-CH_2CH(CH_3)-$, $-CH(CH_3)CH_2-$, $-CH(CH_3)CH(CH_3)-$, $-CH_2C(CH_3)_2-$, $-CH_2CH(C_2H_5)-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH_2CH(C_2H_5)CH_2-$, $-CH_2CH_2CH(C_2H_5)-$, $-C(CH_3)_2CH_2CH_2-$, $-CH(CH_3)CH_2CH(CH_3)-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2C(CH_3)_2CH_2CH_2-$, $-CH_2C(CH_3)_2CH_2-$, $-CH_2CH_2CH(C_2H_5)CH_2-$, $-CH_2CH_2CH_2CH_2CH_2-$, $-CH(CH_3)CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2-$, $-(CH_2)_{10}-$, and the like. Included within this definition are the terms "C_1-C_4 alkylidene" and "C_2-C_4 alkylidene".

The term "C_4-C_8 cycloalkyl" refers to a cycloalkyl ring of four to eight carbon atoms, such as cyclobutyl, cyclopentyl, cyclohexyl, 4,4-dimethylcyclohexyl, cycloheptyl, cyclooctyl, and the like.

The term "straight or branched chain divalent hydrocarbyl residue of one to eight carbon atoms" refers to

a divalent radical derived from a straight or branched alkane, alkene, or alkyne of one to eight carbon atoms. Depending upon the branching and number of carbon atoms, as will be appreciated by organic chemists, such a moiety can contain one, two or three double or triple bonds, or combinations of both. As such, this term can be considered an alkylidene group as defined above containing from 1 to 8 carbon atoms optionally containing one to three double or triple bonds, or combinations of the two, limited as noted in the preceding sentence.

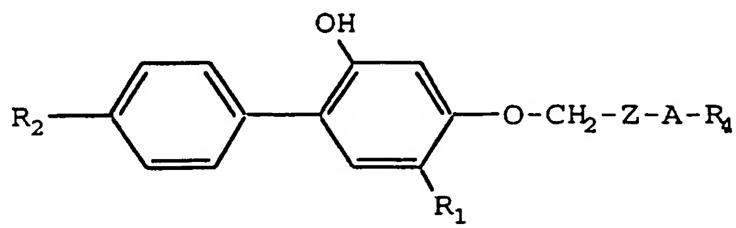
This invention includes the pharmaceutically acceptable base addition salts of the compounds of Formula I. Such salts include those derived from inorganic bases, such as ammonium and alkali and alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, as well as salts derived from basic organic amines, such as aliphatic and aromatic amines, aliphatic diamines, hydroxy alkylamines, and the like. Such bases useful in preparing the salts of this invention thus include ammonium hydroxide, potassium carbonate, sodium bicarbonate, calcium hydroxide, methyl amine, diethyl amine, ethylene diamine, cyclohexylamine, ethanolamine, and the like. The potassium and sodium salt forms are particularly preferred.

This invention includes both mono-salt forms, ie, a 1:1 ratio of a compound of Formula I with a base as previously described, as well as di-salt forms in those instances where a compound of Formula I has two acidic groups. In addition, this invention includes any solvate forms of the compounds of Formula I or salts thereof, such as ethanol solvates, hydrates, and the like.

It is recognized that in compounds having branched alkyl, alkylidenyl, or hydrocarbyl functionality, and in those compounds bearing double or triple bonds, various stereoisomeric products may exist. This invention is not limited to any particular stereoisomer but includes all possible individual isomers and mixtures thereof. The term

"5-tetrazolyl" refers to both tautomers, ie, (1H)-5-tetrazolyl and (2H)-5-tetrazolyl.

A most preferred group of compounds employed in the methods of the present invention are those compounds of Formula Ia:



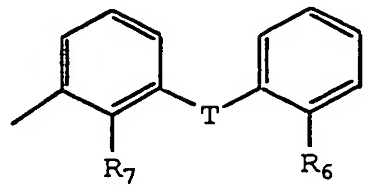
Ia

and pharmaceutically acceptable base addition salts thereof. Especially preferred are those compounds wherein R_2 is halo, particularly fluoro. Preferred R_1 substituents are propyl and especially ethyl.

Preferred Z substituents include C_2-C_4 alkylidene, particularly $-CH_2CH_2-$ and $-CH_2CH_2CH_2CH_2-$. Preferred A groups include -O-, $-CH_2-$, -CH(R_7-substituted phenyl)-, and -$C(CH_3)_2$.

Preferred R_4 groups include -COOH, 5-tetrazolyl, or a mono-, di-, or tri-cyclic group as drawn above wherein there is at least one acidic group attached to a ring, such as -W-COOH, -T-G-COOH, or the corresponding tetrazole derivatives. The preferred W moiety is that of a bond or straight chain C_1-C_4 alkylidene; preferred G moieties are straight chain C_1-C_4 alkylidene. It is preferred that R_5 or R_7 be C_1-C_4 alkyl, especially n-propyl.

Particularly preferred groups are those wherein A is -CH(R_7-substituted phenyl)- and R_4 is -COOH or 5-tetrazolyl. Also preferred are those compounds wherein A is -O- and R_4 is



Preferred aspects of this substructure are those therein R_7 is C_1-C_4 alkyl, especially n-propyl, and R_6 is -W-COOH. Particularly preferred are those compounds wherein T is -O- or -S- and W is a bond.

Particularly preferred compounds of the instant invention include 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid; 3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxy-phenoxy)phenyl)propionic acid; 1-(4-(carboxy-methoxy)phenyl)-1-(1H-tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)hexane; 3-[4-[7-carboxy-9-oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]-propoxy]-9H-xanthene]]propanoic acid; 5-[3-[2-(1-carboxy)-ethyl]-4-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]-propoxy]phenyl]-4-pentynoic acid or a pharmaceutically acceptable salt or solvate thereof.

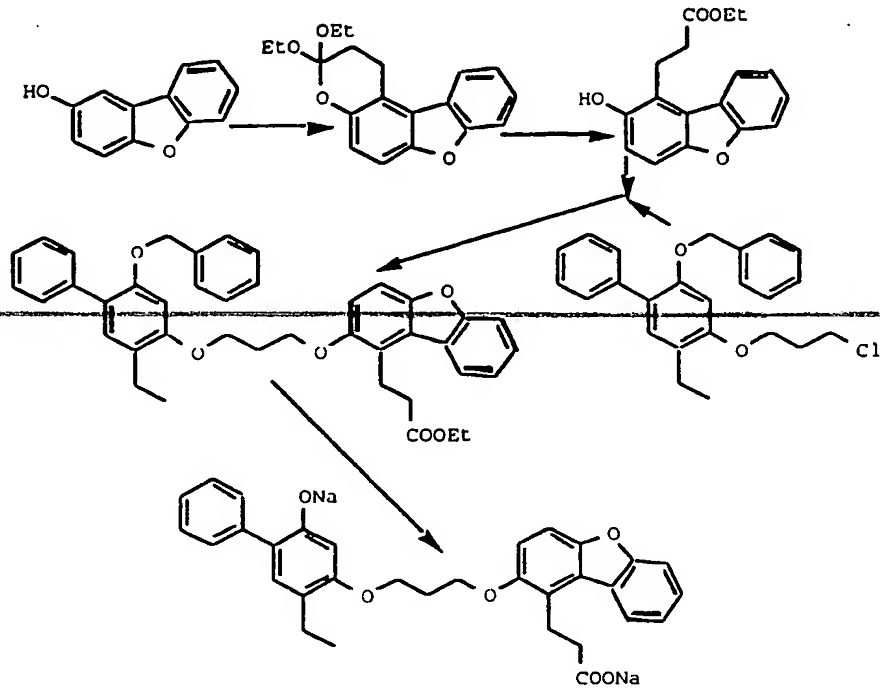
The leukotriene B_4 (LTB_4) antagonists employed in the methods of the present invention may be synthesized essentially as described in US Patent No. 5,462,954 issued October 31, 1995, the entire contents of which are herein incorporated by reference.

The following examples further illustrate the preparation of the intermediates and compounds employed in this invention. The examples are illustrative only and are not intended to limit the scope of the invention. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. NMR spectra were determined on a GE QE-300 spectrometer. All chemical shifts are reported in parts per million (_) relative to tetramethylsilane. Chemical shifts

of aromatic protons of quinoline species in DMSO-d_6 are concentration dependent. The following abbreviations are used to denote signal patterns: s = singlet, d = doublet, t = triplet, q = quartet, b = broad, m = multiplet. Infrared spectra were determined on a Nicolet DX10 FT-IR spectrometer. Mass spectral data were determined on a CEC-21-110 spectrometer using electron impact (EI) conditions, a MAT-731 spectrometer using free desorption (FD) conditions, or a VG ZAB-3F spectrometer using fast atom bombardment (FAB) conditions. Silica gel chromatography was performed using ethyl acetate/hexane gradients unless otherwise indicated. Reverse-phase chromatography was performed on MCI CHP20P gel using an acetonitrile/water or methanol/water gradient unless otherwise indicated. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl immediately prior to use. All reactions were conducted under argon atmosphere with stirring unless otherwise noted. Where structures were confirmed by infra-red, proton nuclear magnetic resonance, or mass spectral analysis, the compound is so designated by "IR", "NMR", or "MS", respectively.

Example 1

3-[2-[3-[(5-Ethyl-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-1-dibenzofuran]propanoic acid disodium salt



A. Preparation of 3,3-diethoxy-2,3-dihydro-1H-benzofuro-[3,2-f][1]benzopyran.

A solution of 2-hydroxydibenzofuran (5.00 g, 27.2 mmol), triethylorthoacrylate (10.1 g, 54.3 mmol) and pivalic acid (1.39 g, 13.6 mmol) in toluene (100 mL) was refluxed for 18 hours. The mixture was cooled to room temperature and washed once with water and once with a saturated sodium bicarbonate solution, dried over sodium sulfate, filtered and concentrated *in vacuo* to provide an orange oil. This material was diluted with hexane and maintained at -20°C for 18 hours. The resulting crystals were collected via vacuum filtration to provide 5.67 g (67%) of the desired title intermediate, mp 64°C; NMR ($CDCl_3$) 7.96 (d, J = 7.8 Hz, 1H),

7.57 (d, J = 8.0 Hz, 1H), 7.46 (t, J = 8 Hz, 1H), 7.35 (m, 2H), 7.06 (d, J = 8.8 Hz, 1H), 3.82 (q, J = 7.2 Hz, 2H), 3.73 (q, J = 6.8 Hz, 2H), 3.35 (t, J = 6.9 Hz, 2H), 2.29 (t, J = 7.0 Hz, 2H), 1.23 (t, J = 7.1 Hz, 6H); MS-FD m/e 312 (p); IR ($CHCl_3$, cm^{-1}) 2982, 1494, 1476, 1451, 1434, 1251, 1090, 1054, 975.

Analysis for $C_{19}H_{20}O_4$:

Calc:	C, 73.06; H, 6.45;
Found:	C, 72.81; H, 6.72.

B. Preparation of 3-[1-(2-hydroxydibenzofuran)]-propanoic acid ethyl ester.

A mixture of 3,3-diethoxy-2,3-dihydro-1H-benzofuro-[3,2-f][1]benzopyran (3.50 g, 11.2 mmol) and 10% aqueous hydrochloric acid (5 mL) in ethyl acetate (30 mL) was stirred at room temperature for 1 hour. The resulting mixture was washed once with water, dried over sodium sulfate, filtered and concentrated *in vacuo* to provide a tan solid. Recrystallization from hexane/ethyl acetate provided 3.11 g (98%) of the desired title intermediate as an off-white crystalline material: mp 128-131°C; NMR ($CDCl_3$) 7.88 (d, J = 7.7 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.47 (t, J = 7.2 Hz, 1H), 7.37 (d, J = 8.9 Hz, 1H), 7.36 (t, J = 6.6 Hz, 1H), 7.13 (d, J = 8.8 Hz, 1H), 7.13 (q, J = 8.8 Hz, 2H), 3.43 (t, J = 5.8 Hz, 2H), 3.01 (t, J = 7.7 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H); MS-FD m/e 284 (100, p), 256 (65), 238 (17); IR (KBr, cm^{-1}) 2985 (b), 1701, 1430, 1226, 1183, 1080.

Analysis for $C_{17}H_{16}O_4$:

Calc:	C, 71.82; H, 5.67;
Found:	C, 71.90; H, 5.43.

C. Preparation of 3-[2-[3-[[5-ethyl-2-(phenylmethoxy)-[1,1'-biphenyl]-4-yl]oxy]propoxy]-1-dibenzofuran]propanoic acid ethyl ester.

3-[1-(2-Hydroxydibenzofuran)]propanoic acid ethyl ester (625 mg, 2.20 mmol) was dissolved in dimethylformamide (10 mL) and carefully treated at room temperature with 95% sodium hydride (58 mg, 2.4 mmol). When gas evolution had ceased, 2-benzyloxy-1-phenyl-5-ethyl-4-(3-chloro-1-propyloxy)benzene (836 mg, 2.20 mmol) was added and the resulting mixture was stirred for 18 hours. The mixture was diluted with ether and washed once with water. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide a dark oil. Silica gel chromatography (ethyl acetate/hexane) provided 200 mg (14%) of the desired titled intermediate as a colorless oil: NMR ($CDCl_3$) 8.11 (d, J = 7.7 Hz, 1H), 7.57 (m, 3H), 7.48 (t, J = 7.3 Hz, 1H), 7.20-7.44 (m, 10 H), 7.17 (s, 1H), 7.08 (d, J = 8.9 Hz, 1H), 6.67 (s, 1H), 5.05 (s, 2H), 4.29 (t, J = 6.2 Hz, 2H), 4.26 (t, J = 6.1 Hz, 2H), 4.15 (q, J = 7.2 Hz, 2H), 3.54 (t, J = 8.5 Hz, 2H), 2.67 (m, 4H), 2.37 (t, J = 6.0 Hz, 2H), 1.21 (m, 6H).

D. Preparation of 3-[2-[3-[(5-ethyl-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-1-dibenzofuran]propanoic acid disodium salt.

To a nitrogen-purged solution of 3-[2-[3-[[5-ethyl-2-(phenylmethoxy)[1,1'-biphenyl]-4-yl]oxy]propoxy]-1-dibenzofuran]propanoic acid ethyl ester (200 mg, 0.318 mmol) in a 1:1 mixture of methanol/tetrahydrofuran (40 mL) was added 10% palladium on carbon (25 mg). The resulting suspension was hydrogenated at 1 atm pressure for 24 hours at room temperature. The mixture was filtered through a short pad of Florisil® and the filtrate concentrated *in vacuo*. The residue was dissolved in a 1:1 mixture of methanol/tetrahydrofuran (20 mL) and treated with 5N sodium hydroxide solution (2 mL) at room temperature for 24 hours. The resulting mixture was extracted once with diethyl ether. The aqueous layer was acidified with 5N hydrochloric acid solution and extracted twice with methylene chloride. The

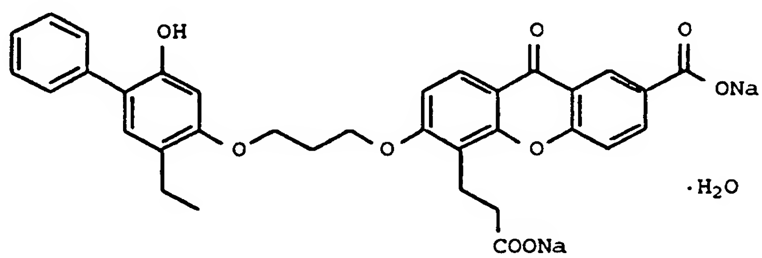
combined methylene chloride fractions were concentrated *in vacuo*. The residue was dissolved in a minimum of 1N sodium hydroxide solution and purified on HP-20 resin to provide 53 mg (30%) of the desired title product as a fluffy white solid: NMR (DMSO-d_6) 8.12 (d, J = 6.9 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.37-7.57 (m, 5H), 7.30 (m, 2H), 7.14 (m, 2H), 6.96 (s, 1H), 6.93 (s, 1H), 4.30 (t, J = 7.3 Hz, 2H), 4.14 (t, J = 5.4 Hz, 2H), 2.48 (m, 4H), 2.23 (m, 4H), 1.10 (t, J = 7.6 Hz, 3H); MS-FAB m/e 555 (88, p + 1), 533 (62); IR ($CHCl_3$, cm^{-1}) 3384 (b), 2969, 1566, 1428, 1257, 1181.

Analysis for $C_{32}H_{28}O_6Na_2$:

Calc:	C, 69.31;	H, 5.09;
Found:	C, 69.51;	H, 5.39.

Example 2

7-Carboxy-9-oxo-3-[3-(2-ethyl-5-hydroxy-4-phenylphenoxy)propoxy]-9H-xanthene-4-propanoic acid disodium salt monohydrate



A mixture of 2-benzyloxy-1-phenyl-5-ethyl-4-(3-chloro-1-propyloxy)benzene (749 mg, 1.97 mmol), ethyl 7-carboethoxy-3-hydroxy-9-oxo-9H-xanthene-4-propanoate (729 mg, 1.97 mmol), potassium carbonate (1.36 g, 9.85 mmol) and potassium iodide (33 mg, 0.20 mmol) was refluxed for 24 hours. Dimethylsulfoxide (2 mL) was added and heating continued for 24 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed once with water. The organic layer was dried over sodium

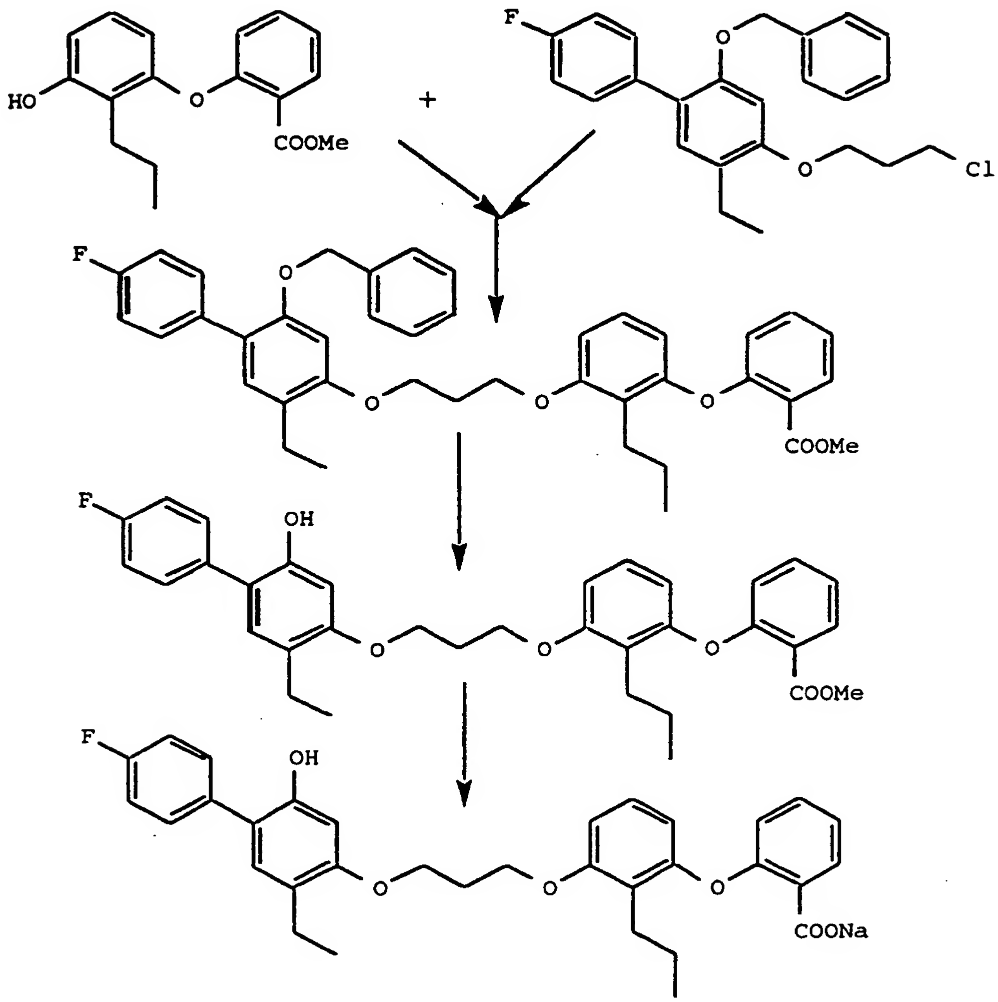
sulfate, filtered and concentrated *in vacuo* to reveal a tan solid. This material was dissolved in ethyl acetate (30 mL) and the resulting solution purged with nitrogen. To this solution was added 10% palladium on carbon (120 mg) and the resulting suspension hydrogenated at 1 atmosphere of pressure. The solution was filtered and concentrated *in vacuo* to provide a colorless oil. This material was dissolved in a solution of 1:1 methanol/tetrahydrofuran (30 mL) and treated with 5N sodium hydroxide solution (2 mL) at room temperature for 18 hours. The resulting solution was extracted once with diethyl ether and the aqueous layer acidified with 5N hydrochloric acid solution. The resulting precipitate was collected via suction filtration. This material was converted to the di-sodium salt and purified as described above for the preparation of Example 1(D) to provide 390 mg (56%) of the desired title product as a fluffy white solid: NMR (DMSO-d_6) 12.65 (s, 1H, -OH), 8.65 (s, 1H), 8.28 (dd, J = 8.5, 2.0 Hz, 1H), 8.01 (d, J = 8.9 Hz, 1H), 7.50 (m, 3H), 7.29 (t, J = 7.8 Hz, 2H), 7.17 (m, 2H), 6.93 (s, 1H), 6.89 (s, 1H), 4.26 (m, 4H), 3.12 (m, 2H), 2.47 (m, 2H), 2.23 (m, 2H), 1.10 (t, J = 7.4 Hz, 3H); MS-FAB m/e 627 (24, p), 605 (40), 583 (24), 331 (24), 309 (100); IR (KBr, cm^{-1}) 3419 (b), 2962, 1612, 1558, 1443, 1390, 1277, 1084.

Analysis for $C_{34}H_{28}O_9Na_2 \cdot H_2O$:

Calc:	C, 63.34; H, 4.69;
Found:	C, 63.36; H, 4.50.

Example 3

2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid sodium salt



A. Preparation of 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-(phenylmethoxy)phenoxy]propoxy]phenoxy]-benzoic acid methyl ester.

A mixture of 2-benzyloxy-1-(4-fluorophenyl)-5-ethyl-4-(3-chloro-1-propyloxy)benzene (20.0 g, 50.2 mmol) and sodium

iodide (75.3 g, 502 mmol) in 2-butanone (200 mL) was refluxed for 6 hours. The mixture was diluted with ether and washed once with water. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide a colorless oil. This material was dissolved in dimethylformamide (100 mL) and treated with 2-(3-hydroxy-2-propylphenoxy)benzoic acid methyl ester (14.4 g, 50.2 mmol) and potassium carbonate (20.8 g, 151 mmol) at room temperature for 24 hours. This mixture was diluted with water and twice extracted with ether. The aqueous layer was separated and back-extracted once with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide a yellow oil. Silica gel chromatography provided 25.4 g (78%) of the desired title intermediate as a pale golden oil: NMR ($CDCl_3$) 7.91 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 8.6 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.25-7.43 (m, 6H), 7.03-7.38 (m, 5H), 6.84 (d, J = 8.3 Hz, 1H), 6.71 (d, J = 8.1 Hz, 1H), 6.63 (s, 1H), 6.47 (d, J = 8.1 Hz, 1H), 5.03 (s, 2H), 4.24 (t, J = 5.7 Hz, 2H), 4.21 (t, J = 5.8 Hz, 2H), 3.86 (s, 3H), 2.69 (t, J = 7.8 Hz, 2H), 2.64 (t, J = 7.7 Hz, 2H), 2.34 (quintet, J = 6.0 Hz, 2H), 1.60 (hextet, J = 5.0 Hz, 2H), 1.22 (t, J = 7.5 Hz, 3H), 0.94 (t, J = 7.5 Hz, 3H); MS-FD m/e 648 (p); IR ($CHCl_3$, cm^{-1}) 2960, 1740, 1604, 1497, 1461, 1112.

Analysis for $C_{41}H_{41}O_6F$:

Calc:	C, 75.91; H, 6.37;
Found:	C, 76.15; H, 6.45.

B. Preparation of 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid methyl ester.

2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-(phenylmethoxy)phenoxy]propoxy]phenoxy]benzoic acid methyl ester (33.0 g, 50.9 mmol) was de-benzylated as described

above for the preparation of Example 2 to provide 27.3 g (96%) of the title intermediate as an amber oil: NMR ($CDCl_3$) 7.90 (dd, J = 7.8, 1.7 Hz, 1H), 7.42 (m, 3H), 7.05-7.23 (m, 4H), 6.99 (s, 1H), 6.84 (d, J = 8.1 Hz, 1H), 6.70 (d, J = 8.1 Hz, 1H), 6.55 (s, 1H), 6.46 (d, J = 8.1 Hz, 1H), 5.05 (s, 1H, -OH), 4.23 (m, 4H), 3.86 (s, 3H), 2.68 (t, J = 7.4 Hz, 2H), 2.62 (q, J = 7.5 Hz, 2H), 2.36 (quintet, J = 6.0 Hz, 2H), 1.60 (hextet, J = 7.7 Hz, 2H), 1.20 (t, J = 7.6 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H); MS-FD m/e 558 (p); IR ($CHCl_3$, cm^{-1}) 2965, 1727, 1603, 1496, 1458, 1306, 1112.

Analysis for $C_{34}H_{35}O_6F$:

Calc: C, 73.10; H, 6.31;

Found: C, 73.17; H, 6.42.

C. Preparation of 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid sodium salt.

2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid methyl ester (21.5 g, 38.5 mmol) was hydrolyzed as described above for the preparation of Example 2. The acid was converted to the sodium salt and purified as described above for the preparation of Example 1(D) to provide 16.7 g (77%) of the desired title product as a white amorphous solid: NMR (DMSO-d_6) 10.50 (bs, 1H, -OH), 7.51 (m, 3H), 7.20 (t, J = 7.4 Hz, 1H), 7.13 (m, 2H), 7.00 (m, 2H), 6.95 (s, 1H), 6.67 (dd, J = 8.2, 3.3 Hz, 2H), 6.62 (s, 1H), 6.26 (d, J = 8.2 Hz, 1H), 4.14 (t, J = 5.8 Hz, 2H), 4.02 (t, J = 5.7 Hz, 2H), 2.60 (t, J = 6.8 Hz, 2H), 2.47 (q, J = 7.3 Hz, 2H), 2.16 (t, J = 5.9 Hz, 2H), 1.45 (hextet, J = 7.5 Hz, 2H), 1.07 (t, J = 7.5 Hz, 3H), 0.81 (t, J = 7.4 Hz, 3H); MS-FAB m/e 568 (38, p + 1), 567 (100, p), 544 (86), 527 (77), 295 (65), 253 (45); IR (KBr, cm^{-1}) 3407 (b), 2962, 1603, 1502, 1446, 1395, 1239, 1112.

Analysis for $C_{33}H_{32}O_6FNa$:

Calc: C, 69.95; H, 5.69; F, 3.35;
Found: C, 69.97; H, 5.99; F, 3.52.

The methods of the present invention describe the use of leukotriene antagonists for the inhibition and treatment of ischemia reperfusion injury which is characterized by the excessive release of leukotriene B_4.

The term "excessive release" of a leukotriene refers to an amount of the leukotriene sufficient to cause ischemia reperfusion injury. The amount of leukotriene which is considered to be excessive will depend on a variety of factors, including the amount of leukotriene required to cause the disease, and the species of the mammal involved. As will be appreciated by those skilled in the art, the success of treating a mammal suffering from ischemia reperfusion injury by an excessive release of leukotriene with a compound of Formula I will be measured by the regression or prevention of the symptoms of the condition.

Assays

Assay 1

The effectiveness of compounds of Formula I to inhibit the binding of tritiated LTB_4 to guinea pig lung membranes was determined as follows.

$[^3H]$-LTB_4 Radioligand Binding Assay in Guinea Pig Lung Membranes

$[^3H]$-LTB_4 (196-200 Ci/mmole) was purchased from New England Nuclear (Boston, MA). All other materials were purchased from Sigma (St. Louis, MO). Incubations (555 mL) were performed in polypropylene minitubes for 45 minutes at 30°C and contained 25 mg of guinea pig lung membrane protein (Silbaugh, et al., European Journal of Pharmacology, 223 (1992) 57-64) in a buffer containing 25 mM MOPS, 10 mM

$MgCl_2$, 10 mM $CaCl_2$, pH 6.5, approximately 140 pM $[^3H]$-LTB_4, and displacing ligand or vehicle (0.1% DMSO in 1 mM sodium carbonate, final concentration) as appropriate. The binding reaction was terminated by the addition of 1 mL ice cold wash buffer (25 mM Tris-HCl, pH 7.5) followed immediately by vacuum filtration over Whatman GF/C glass fiber filters using a Brandel (Gaithersburg, MD) 48 place harvester. The filters were washed three times with 1 mL of wash buffer. Retained radioactivity was determined by liquid scintillation counting at 50% counting efficiency using Ready Protein Plus cocktail (Beckman, Fullerton, CA). Nondisplaceable binding was determined in the presence of 1 mM LTB_4 and was usually less than 10% of total binding. Data were analyzed using linear regression analysis of log-logit plots of the values between 10% and 90% of control binding to calculate IC_{50}s and slope factors (pseudo-Hill coefficients). IC_{50} values thus obtained were corrected for radioligand concentration (Cheng and Prusoff, Biochem. Pharmacol., 22, 3099 (1973)) to calculate K_i values. pKi is the mean -log K_i for n experiments.

Compounds of the instant invention tested in the above assay were found to have a pKi of between 7 and 10.

The ability of a compound of formula I to ameliorate tissue damage caused by an ischemia-reperfusion insult in different tissues can be demonstrated in a variety of animal species. The methodology for showing protective action in splanchnic ischemia/reperfusion injury in rats is an example (Karasawa et al., Am. J. Physiol., 261, G191-8,1991).

Assay 2

In this circulatory shock model, ischemia is induced by clamping both the celiac and superior mesenteric arteries with atraumatic arterial clamps. Immediately after occlusion, rats are given heparin (500 U/kg i.v.). The clamps are removed after 90 minutes and splanchnic vascular

reperfusion allowed to proceed. Animals are followed for an additional 2 hours or until the mean arterial blood pressure (MABP) falls below 45 mmHg. Survival time is the period from removal of the clamps to the time MABP falls below 45 mmHg. Survivors are defined as animals that maintain a MABP of 45 mmHg for 120 min after reperfusion. A dose response is obtained by dividing the animals into 5 experimental groups of 10 rats each. The groups are: sham-treated rats given vehicle: occluded-reperfused (O/R) rats given vehicle; O/R rats given 1, 3, or 10 mg/kg of compound intravenously 10 minutes before reperfusion. At the end of the experiment, blood is withdrawn for analysis of tissue breakdown products such as plasma free amino-nitrogen and myocardial depressant factor (MDF). Also, a 5-cm piece of ileal tissue is excised about 30 cm distal from the stomach and analyzed for myeloperoxidase activity, a marker for neutrophil infiltration. The effectiveness of a treatment is accessed by comparing survival time, percent survivors, free amino-nitrogen concentration, MDF concentration and ileum MPO activity of the treated group to that of a vehicle control.

The therapeutic and prophylactic treatments provided by this invention are practiced by administering to a mammal in need thereof a dose of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof, that is effective to inhibit or treat ischemia reperfusion injury.

The term "inhibit" includes its generally accepted meaning which includes prohibiting, preventing, restraining and slowing, stopping or reversing progression, severity or a resultant symptom. As such, the present method includes both medical therapeutic and/or prophylactic administration as appropriate.

While it is possible to administer a compound employed in the methods of this invention directly without any formulation, the compounds are usually administered in the form of pharmaceutical formulation comprising a pharmaceutically acceptable excipient and at least one

compound of the present invention. The compounds or formulations of the present invention may be administered by the oral and rectal routes, topically, parenterally, e.g., by injection and by continuous or discontinuous intra-arterial infusion, in the form of, for example, tablets, lozenges, sublingual tablets, sachets, cachets, elixirs, gels, suspensions, aerosols, ointments, for example, containing from 0.01 to 90% by weight of the active compound in a suitable base, soft and hard gelatin capsules, suppositories, injectable solutions and suspensions in physiologically acceptable media, and sterile packaged powders adsorbed onto a support material for making injectable solutions. Such formulations are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. See, e.g., REMINGTON'S PHARMACEUTICAL SCIENCES, (16th ed. 1980).

In making the formulations employed in the present invention the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient.

In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable carriers, excipients and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate,

microcrystalline cellulose, polyvinylpyrrolidone, cellulose, tragacanth, gelatin, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxybenzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compounds of this invention may be delivered transdermally using known transdermal delivery systems and excipients. Most preferably, a compound of this invention is admixed with permeation enhancers including, but not limited to, propylene glycol, polyethylene glycol monolaurate, and azacycloalkan-2-ones, and incorporated into a patch or similar delivery system. Additional excipients including gelling agents, emulsifiers, and buffers may be added to the transdermal formulation as desired.

For topical administration, a compound of this invention ideally can be admixed with any variety of excipients in order to form a viscous liquid or cream-like preparation.

For oral administration, a compound of this invention ideally can be admixed with carriers and diluents and molded into tablets or enclosed in gelatin capsules.

In the case of tablets, a lubricant may be incorporated to prevent sticking and binding of the powdered ingredients in the dies and on the punch of the tableting machine. For such purpose there may be employed for instance aluminum, magnesium or calcium stearates, talc or mineral oil.

Preferred pharmaceutical forms of the present invention parenteral, capsules and tablets.

The therapeutic and prophylactic treatments provided by this invention are practiced by administering to a mammal in need thereof a dose of a compound of formula I or a

pharmaceutically acceptable salt or solvate thereof that is effective to inhibit or treat ischemia reperfusion injury.

Advantageously for this purpose, formulations may be provided in unit dosage form, preferably each dosage unit containing from about 5 to about 500 mg (from about 5 to 50 mg in the case of parenteral or inhalation administration, and from about 25 to 500 mg in the case of oral or rectal administration) of a compound of Formula I. Dosages from about 0.5 to about 300 mg/kg per day, preferably 0.5 to 20 mg/kg, of active ingredient may be administered although it will, of course, readily be understood that the amount of the compound or compounds of Formula I actually to be administered will be determined by a physician, in the light of all the relevant circumstances including the condition to be treated, the choice of compound to be administered and the choice of route of administration and therefore the above preferred dosage range is not intended to limit the scope of the present invention in any way.

The specific dose of a compound administered according to this invention to obtain therapeutic or prophylactic effects will, of course, be determined by the particular circumstances surrounding the case, including, for example, the route of administration the age, weight and response of the individual patient, the condition being treated and the severity of the patient's symptoms.

In general, the compounds of the invention are most desirably administered at a concentration that will generally afford effective results without causing any serious side effects and can be administered either as a single unit dose, or if desired, the dosage may be divided into convenient subunits administered at suitable times throughout the day.

While all of the compounds illustrated above exemplify LTB_4 inhibition activity in vitro, we have also discovered that compounds bearing a single acidic group (R_6) are considerably more orally bioactive when administered to mammals compared with those compounds bearing two such

acidic groups. Thus, a preferred embodiment when administering compounds of Formula I orally to mammals comprises administering compounds bearing a single acidic R_6 functionality.

The following formulation examples may employ as active compounds any of the compounds of this invention. The examples are illustrative only and are not intended to limit the scope of the invention in any way.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxyphenoxy)phenyl)propanoic acid	250
Starch	200
Magnesium stearate	10

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
1-(4-(Carboxymethoxy)phenyl)-1-(1H-tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)hexane	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Magnesium stearate	5

The components are blended and compressed to form tablets each weighing 665 mg.

Formulation 3

An aerosol solution is prepared containing the following components:

	Weight %
3-[4-[7-Carboxy-9-oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-9H-xanthene]]propanoic acid	0.25
Ethanol	30.00
Propellant 11 (trichlorofluoromethane)	10.25
Propellant 12 (Dichlorodifluoromethane)	29.75
Propellant 114 (Dichlorotetrafluoroethane)	29.75

The active compound is dissolved in the ethanol and the solution is added to the propellant 11, cooled to -30°C. and transferred to a filling device. The required amount is then

fed to a container and further filled with the pre-mixed propellants 12 and 114 by means of the cold-filled method or pressure-filled method. The valve units are then fitted to the container.

Formulation 4

Tablets each containing 60 mg of active ingredient are made up as follows:

2-[2-Propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]-benzoic acid sodium salt	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50-60° and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation 5

Capsules each containing 80 mg of medicament are made as follows:

5-[3-[2-(1-Carboxy)ethyl]-4-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-phenyl]-4-pentynoic acid	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	2 mg
Total	200 mg

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

Formulation 6

Suppositories each containing 225 mg of active ingredient are made as follows:

5-[3-[2-(1-Carboxy)ethyl]-4-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-phenyl]-4-pentynoic acid	225 mg
Unsaturated or saturated fatty acid glycerides to	2,000 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

Formulation 7

Suspensions each containing 50 mg of medicament per 5 mL dose are made as follows:

2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid	50 mg
Sodium carboxymethyl cellulose	50 mg
Sugar	1 g
Methyl paraben	0.05 mg
Propyl paraben	0.03 mg
Flavor	q.v.
Color	q.v.
Purified water to	5 mL

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethylcellulose, sugar, and a portion of the water to form a suspension. The parabens, flavor and color are dissolved and diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 8

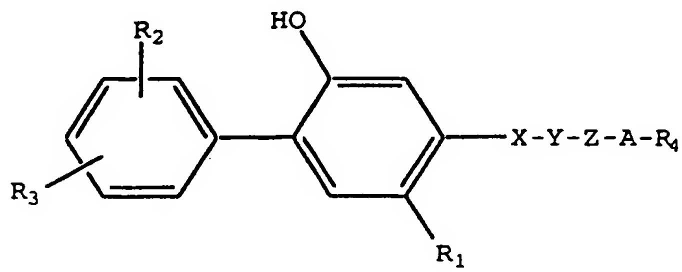
An intravenous formulation may be prepared as follows:

2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid	100 mg
Isotonic saline	1,000 ml

The solution of the above ingredients generally is administered intravenously to a subject at a rate of 1 ml per minute.

We claim:

1. A method for inhibiting or treating ischemia reperfusion injury in a mammal which comprises administering to a mammal in need thereof an effective amount of a compound of the formula I



I

wherein:

R_1 is C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, C_1-C_4 alkoxy, (C_1-C_4 alkyl)thio, halo, or R_2-substituted phenyl;

each R_2 and R_3 are each independently hydrogen, halo, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, (C_1-C_4 alkyl)-$S(O)_q$-, trifluoromethyl, or di-(C_1-C_3 alkyl)amino;

X is -O-, -S-, -C(=O), or -CH_2-;

Y is -O- or -CH_2-;

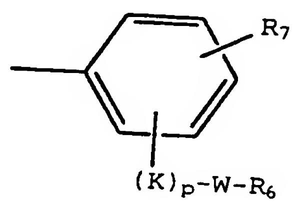
or when taken together, -X-Y- is -CH=CH- or

$$—C \equiv C— \quad ;$$

Z is a straight or branched chain C_1-C_{10} alkylidenyl;

A is a bond, -O-, -S-, -CH=CH-, or $-CR_aR_b-$, where R_a and R_b are each independently hydrogen, C_1-C_5 alkyl, or R_7-substituted phenyl, or when taken together with the carbon atom to which they are attached form a C_4-C_8 cycloalkyl ring;

R_4 is R_6 ,



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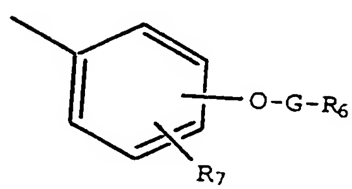

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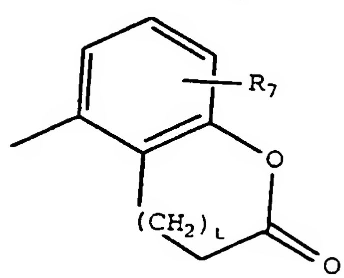

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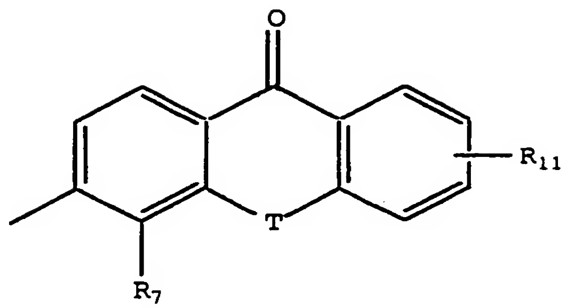

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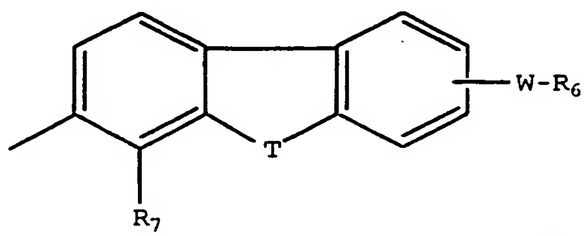

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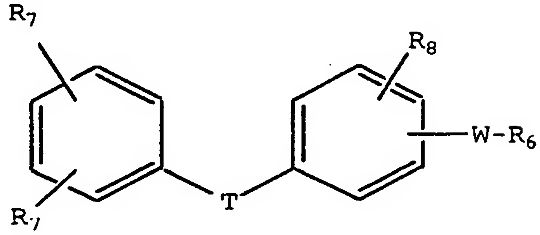


where,

each R_6 is independently -COOH, 5-tetrazolyl, $-CON(R_9)_2$, or $-CONHSO_2R_{10}$;

each R_7 is hydrogen, C_1-C_4 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, benzyl, methoxy, $-W-R_6$, $-T-G-R_6$, (C_1-C_4 alkyl)-T-(C_1-C_4 alkylidenyl)-O-, or hydroxy;

R_8 is hydrogen or halo;

each R_9 is independently hydrogen, phenyl, or C_1-C_4 alkyl, or when taken together with the

nitrogen atom form a morpholino, piperidino, piperazino, or pyrrolidino group;

R_{10} is C_1-C_4 alkyl or phenyl;

R_{11} is R_2, -W-R_6, or -T-G-R_6;

each W is a bond or straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

each G is a straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

each T is a bond, -CH_2-, -O-, -NH-, -NHCO-, -C(=O)-, or -S(O)$_q$-;

K is -C(=O)- or -CH(OH)-;

each q is independently 0, 1, or 2;

p is 0 or 1; and

t is 0 or 1;

provided when X is -O- or -S-, Y is not -O-;

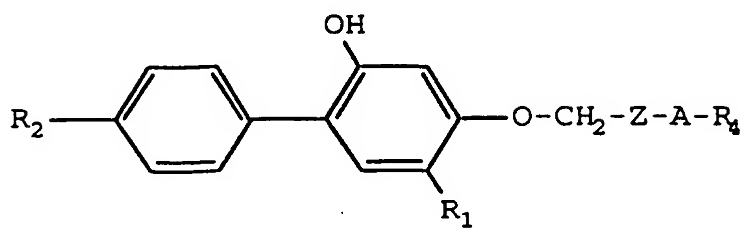
provided when A is -O- or -S-, R_4 is not R_6;

provided when A is -O- or -S- and Z is a bond, Y is not -O-; and

provided W is not a bond when p is 0;

or a pharmaceutically acceptable salt or solvate thereof.

2. The method as claimed in **Claim 1** employing a compound of the formula



or a pharmaceutically acceptable salt or solvate thereof.

3. The method as claimed in **Claim 2** employing 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid or a pharmaceutically acceptable salt or solvate thereof.

4. The method as claimed in **Claim 2** employing 3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxy-phenoxy)phenyl)propionic acid or a pharmaceutically acceptable salt or solvate thereof.

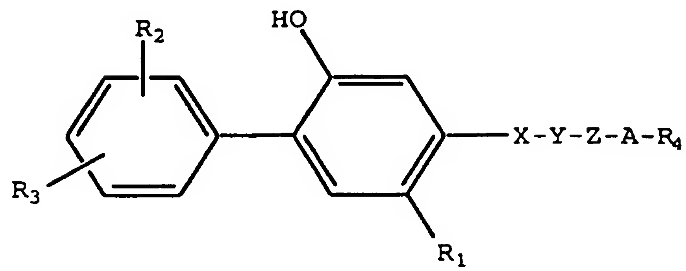
5. The method as claimed in **Claim 2** employing 1-(4-(carboxy-methoxy)phenyl)-1-(1H-tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)hexane or a pharmaceutically acceptable salt or solvate thereof.

6. The method as claimed in **Claim 2** employing 3-[4-[7-carboxy-9-oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]-propoxy]-9H-xanthene]]propanoic acid or a pharmaceutically acceptable salt or solvate thereof.

7. The method as claimed in **Claim 2** employing 5-[3-[2-(1-carboxy)-ethyl]-4-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]-propoxy]phenyl]-4-pentynoic acid or a pharmaceutically acceptable salt or solvate thereof.

8. The method as claimed in any one of **Claims 1 to 7** in which the mammal is a human.

9. Use of a compound of the formula I



I

wherein:

R_1 is C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, C_1-C_4 alkoxy, (C_1-C_4 alkyl)thio, halo, or R_2-substituted phenyl;

each R_2 and R_3 are each independently hydrogen, halo, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, (C_1-C_4 alkyl)-$S(O)_q$-, trifluoromethyl, or di-(C_1-C_3 alkyl)amino;

X is -O-, -S-, -C(=O), or $-CH_2-$;

Y is -O- or $-CH_2-$;

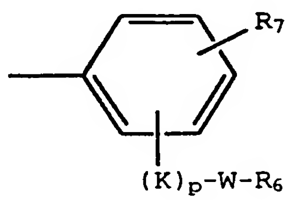
or when taken together, -X-Y- is -CH=CH- or

$$—C\equiv C— \quad ;$$

Z is a straight or branched chain C_1-C_{10} alkylidenyl;

A is a bond, -O-, -S-, -CH=CH-, or $-CR_aR_b-$, where R_a and R_b are each independently hydrogen, C_1-C_5 alkyl, or R_7-substituted phenyl, or when taken together with the carbon atom to which they are attached form a C_4-C_8 cycloalkyl ring;

R_4 is R_6 ,



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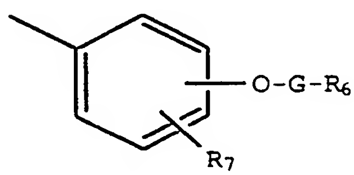

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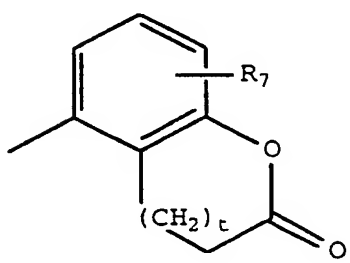

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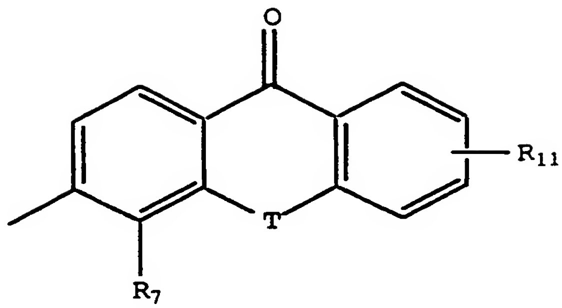

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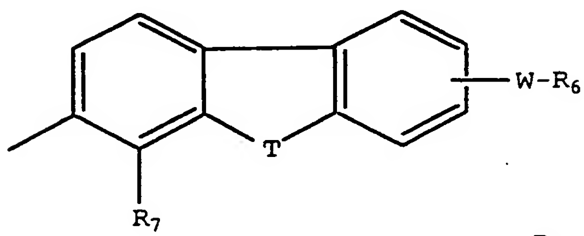

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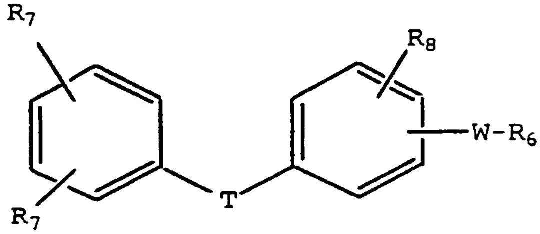


where,

each R_6 is independently -COOH, 5-tetrazolyl, $-CON(R_9)_2$, or $-CONHSO_2R_{10}$;

each R_7 is hydrogen, C_1-C_4 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, benzyl, methoxy, $-W-R_6$, $-T-G-R_6$, (C_1-C_4 alkyl)-T-(C_1-C_4 alkylidenyl)-O-, or hydroxy;

R_8 is hydrogen or halo;

each R_9 is independently hydrogen, phenyl, or C_1-C_4 alkyl, or when taken together with the

nitrogen atom form a morpholino, piperidino, piperazino, or pyrrolidino group;

R_{10} is C_1-C_4 alkyl or phenyl;

R_{11} is R_2, $-W-R_6$, or $-T-G-R_6$;

each W is a bond or straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

each G is a straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

each T is a bond, $-CH_2-$, -O-, -NH-, -NHCO-, -C(=O)-, or $-S(O)_q-$;

K is -C(=O)- or -CH(OH)-;

each q is independently 0, 1, or 2;

p is 0 or 1; and

t is 0 or 1;

provided when X is -O- or -S-, Y is not -O-;

provided when A is -O- or -S-, R_4 is not R_6;

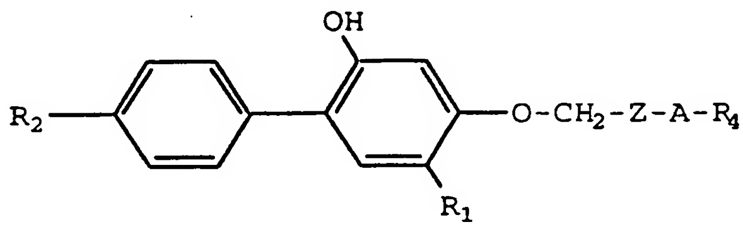
provided when A is -O- or -S- and Z is a bond, Y is not -O-; and

provided W is not a bond when p is 0;

or a pharmaceutically acceptable salt or solvate thereof, optionally in combination with a pharmaceutically acceptable excipient, for the preparation of a pharmaceutical

composition for inhibiting or treating ischemia reperfusion injury in a mammal.

10. The use according to claim 9 employing a compound of the formula;



or a pharmaceutically acceptable salt or solvate thereof.

11. The use according to claim 9 wherein the compound employed is 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid or a pharmaceutically acceptable salt or solvate thereof.

12. The use according to claim 9 wherein the compound employed is 3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxy-phenoxy)phenyl)propionic acid or a pharmaceutically acceptable salt or solvate thereof.

13. The use according to claim 9 wherein the compound employed is 1-(4-(carboxy-methoxy)phenyl)-1-(1H-tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)hexane or a pharmaceutically acceptable salt or solvate thereof.

14. The use according to claim 9 wherein the compound employed is 3-[4-[7-carboxy-9-oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]-propoxy]-9H-xanthene]]propanoic acid or a pharmaceutically acceptable salt or solvate thereof.

15. The use according to claim 9 wherein the compound employed is 5-[3-[2-(1-carboxy)-ethyl]-4-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]-propoxy]phenyl]-4-pentynoic acid or a pharmaceutically acceptable salt or solvate thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/05478

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/52, 31/41, 31/19
US CL :514/263, 381, 568, 570
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/263, 381, 568, 570

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 5,462,954 A (BAKER et al.) 31 October 1995, see column 1, line 39 - column 3, line 20 and column 135, line 53 - column 137, line 24.	9-15 ------ 1-8
Y	US 5,492,915 A (DEREU et al.) 20 February 1996, see column 1, lines 59-67.	1-8
Y	US 5,457,124 A (COHEN et al.) 10 October 1995, see column 1, lines 50-60.	1-8

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 APRIL 1998	28 JUL 1998

Name and mailing address of the ISA/US	Authorized officer
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